(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/97796 A1

(51) International Patent Classification[7]: A61K 31/05, 47/48

(21) International Application Number: PCT/IN00/00124

(22) International Filing Date:
14 December 2000 (14.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
573/MUM/2000 21 June 2000 (21.06.2000) IN

(71) Applicant *(for all designated States except US)*: **BHARAT SERUMS & VACCINES LTD.** [IN/IN]; Plot A-371/A-372, Road No. 27, Wagle Estate, Thane 400 604 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PAI, Srikanth** [IN/IN]; Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate, Thane 400 604 (IN). **RIVANKAR, Sangeeta** [IN/IN]; Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate, Thane 400 604 (IN). **KOCHAREKAR, Shilpa** [IN/IN]; Bharat Serums & Vaccines Ltd., Road No. 27, Wagle Estate, Thane 400 604 (IN).

(74) Agent: **KASBEKAR, Madhav**; 48/3, Madhavi Sah- Niwas, 277, Mogul Lane, Mahim, Mumbai 400 016 (IN).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GH, GM, HR, HU, ID, IL, JP, KE, KP, KR, KZ, LK, LU, MA, MD, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/97796 A1

(54) Title: CLEAR AQUEOUS ANAESTHETIC COMPOSITION

(57) Abstract: Sterile pharmaceutical stable autoclaved clear aqueous compositions of propofol (2,6-Diisopropyl phenol) suitable for parenteral administration are described. The compositions essentially consist of a complex of propofol with 2-hydroxypropyl-β-cyclodextrin in a weight ratio of 1:30 - 1:60. This complex of propofol with 2-hydroxypropyl-β-cyclodextrin produces a clear aqueous composition that is stable to autoclaving. The composition is effective as an anaesthetic agent. The process of making these synergistic compositions has been described.

CLEAR AQUEOUS ANAESTHETIC COMPOSITION

Field of the Invention

This invention relates to a pharmaceutical composition of propofol, (2,6-diisopropyl phenol) for parenteral administration. This invention is particularly related to the compositions in which propofol is complexed with 2-hydroxypropyl-β-cyclodextrin (referred to hereinafter as "HPBCD"). This invention is more particularly related to a clear aqueous composition of the propofol - HPBCD complex that is stable to autoclaving and the process to prepare the same.

Background of the Invention :

Propofol is an intravenous anesthetic agent characterised by a short recovery time. It has the desirable property of rapid onset and offset of the anaesthetic effect following intravenous administration and minimal accumulation on long-term administration.

Propofol even though is a preferred anesthetic agent, has posed a big challenge to the formulator since its invention because of its aqueous insolubility. It was at first formulated as a 1% aqueous solution containing nonionic surfactant Cremophor EL as a solubiliser. However, Cremophor EL has been implicated in some adverse reactions when administered intravenously, including anaphylactoid reactions.

Subsequently, the anaesthetic agent was formulated as oil-in-water emulsion containing 1% w/v propofol with 10% w/v soybean oil & 1.2% w/v purified egg phosphatide. Lipid based emulsions suffer from several limitations such as poor physical stability, the potential for embolism, pain on injection and increased fat load. Furthermore, strict aseptic techniques must be maintained when handling these formulations since they contain no antimicrobial preservatives and therefore can support rapid growth of microogranisms.

G. Trapani et al (J.P.S. April 1998, 87(4), 514-518) have studied the physicochemical and anaesthetic properties of a freeze dried inclusion complex of propofol with 2-hydroxypropyl-β-cyclodextrin in 1:1mol/mol (1:8 wt./wt.) stoichiometry. In this process, complex formation was achieved after continued stirring for five days.

Pharmaceutical compositions comprising inclusion complex of propofol and 2-hydroxypropyl-β-cyclodextrin have been described in a WO 96/32135. At the ratio of propofol to 2-hydroxypropyl-β-cyclodextrin 1:1.5 to 1:<2 mol/mol (1:11.79 to 1:<15.72 wt./wt.), additional co-solvent was necessary to formulate a clear colourless solution. At 1:2 to 1:2.5 mol/mol stoichiometry (1:15.72 to 1:19.65 wt./wt.) solution was clear. However we find that such solutions are not stable to autoclaving.

Preferred process of sterilisation specified in pharmacopoeias is autoclaving of the product in the final container. Further as propofol is commonly administered by intravenous route to induce and maintain general anaesthesia, terminal sterilisation is the only preferred alternative which offers higher confidence of sterility compliance.

Our main objective of this invention is thus to develop a clear aqueous composition of propofol complexed with HPBCD that is stable to autoclaving thereby making it suitable for parenteral administration in human beings and other mammals.

Summary of the Invention

Accordingly, the present invention relates to an autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration comprising propofol and 2- hydroxypropyl - β - cyclodextrin (HPBCD) in a wt. ratio of propofol : HPBCD from about1:30 to about 1:60.

The composition of the present invention further comprises other conventional additives as required by parenteral dosage form.

The present invention further relates to a process for preparing an autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral dministration comprising steps of

i) addition of propofol as such or in a solution form to solution of 2-hydroxypropyl-β-cyclodextrin (HPBCD) either in water or other solvents in a wt. ratio of propofol : HPBCD from about 1:30 to about 1:60 under stirring;

ii) keeping said solution of propofol and HPBCD under intimate contact till complexation of propofol with HPBCD is complete to obtain a clear bulk solution;

iii) removing the said solvent if other than water and adding water;

iv) making up the volume with water to a required concentration of propofol in said composition obtained at the end of step (iii);

v) filtering the said composition obtained at the end of step (iv) through 2μ to 0.2μ filter;

vi) filling the said filtrate obtained at the end of step (v) in containers such as vials, ampoules, followed by nitrogen purging and sealing the filled containers;

vii) autoclaving the sealed containers filled with said filtrate.

The present invention also relates to an autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as described herein and made by the process of the present invention as described above .

Detailed description of embodiments of the invention :

The different embodiments of the invention described below are applicable to the product to the process of making the product and for the product made by the process. The propofol content of the composition of this process of invention is from about 1mg/ml to about 20mg/ml, preferably from about 2mg/ml to about10mg/ml, more preferably about 10mg/ml and about 2mg/ml. The 10mg/ml composition is suitable as bolus injection and requires to be diluted if used for continuous infusion. However, 2mg/ml composition is suitable for continuous infusion and requires no dilution before administration.

The preferred wt./wt. ratio of propofol to HPBCD is from about 1:30 to about 1:45. The more preferred wt./wt. ratio is about 1:30.

The conventional additives which may be used in the process of this invention contain commonly used additives such as anticrystallising agents, antioxidants, buffers and isotonic diluents, which in the usual quantities added do not affect to the clarity and stability of the composition.

Anticrystallising agents are selected from a group of pharmaceutically acceptable compounds such as Glycerin, Propylene glycol, Polyethylene glycol of low molecular weight series. Preferably the anticrystallising agent used is Glycerin.

Antioxidants are selected from a group of pharmaceutically acceptable compounds such as Ethylene diamine tetraacetic acid and salts thereof, Sodium metabisulphite, Acetylcysteine, Ascorbic acid. Preferably the antioxidant used is Disodium edetate

Buffers are selected from a group of pharmaceutically acceptable buffer systems such as Phosphate buffer, Citrate buffer, Glycine buffer containing any of the commonly used compounds or a mixture of compounds such as Citric acid, Sodium citrate, Potassium citrate, Glycine, Phosphoric acid, Sodium phosphate, Disodium hydrogen phosphate, Sodium dihydrogen phosphate, Potassium phosphate, Dipotassium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium hydroxide, Potassium hydroxide, Hydrochloric acid. Preferably the buffer used is a mixture of Potassium dihydrogen phosphate and Sodium hydroxide.

Isotonic diluents are selected from a group of pharmaceutically acceptable diluents such as Dextrose solution and Sodium chloride solution. Preferably the isotonic diluent used is Dextrose solution.

In this process of invention, propofol is added as such for complexation with HPBCD solution or it is added as a solution in pharmaceutically acceptable organic solvent(s) and the solvent is removed from the system after the complexation is complete. Organic solvents are selected from a group of solvents such as Ethanol, Methanol and Isopropyl alcohol or a mixture thereof. Preferably the organic solvent used is Ethanol.

HPBCD is dissolved in water for complexing with propofol. Alternatively HPBCD is dissolved in pharmaceutically acceptable organic solvents and the solvent is removed from the system after the complexation is complete. Organic solvents used are Ethanol, Methanol or a mixture thereof. Preferably the organic solvent used is Ethanol.

In the process of present invention, complexation of propofol with HPBCD is brought about by intimate contact of these two ingredients. The complexation of propofol with HPBCD is carried out at a temperature of about 10°C to about 50°C, preferably at ambient temperature.

In the process of present invention there are four modes of adding propofol to HPBCD solution;

	Propofol	HPBCD
1)	As such	Solution in water
2)	Solution in organic solvent	Solution in water
3)	As such	Solution in organic solvent
4)	Solution in organic solvent	Solution in organic solvent

In the first mode of addition, since propofol is not soluble in water, the intimate contact is brought about by mixing using conventional stirrers. Faster complexation is achieved when high shear mixer, colloid mill or high pressure homogeniser is used for bringing about intimate contact.

In second, third and fourth mode of addition, the organic solvent is removed totally under vacuum preferably at the temperature of less than 50°C.

In the third and fourth mode of addition, the residue obtained after total removal of organic solvent is dissolved in water or water containing additives.

The compositions prepared by the process of the present invention are specifically clear aqueous solutions prepared under controlled conditions as required for parenteral dosage form.

The process of the present invention gives a clear aqueous composition of propofol, which is advantageous in terms of no added fat load, no adverse reactions of emboli, no pain on injection, improved stability and a scope for visual inspection before administration in view of its clarity.

The process of the present invention also offers the advantage of terminal sterilisation in the final container which is the preferred process specified in pharmacopoeias. Further as the process of the present invention gives a composition of propofol that is commonly administered by intravenous route, the terminal sterilisation is the only preferred alternative which offers higher confidence of sterility compliance. Terminal sterilisation offers further advantage of parametric release, that is the release of the batch of sterilised products based on process data rather than on the basis of submitting a sample of the items to sterility testing.

The process of the present invention gives a composition that is suitable as a ready marketable product. Acute toxicity study in mice carried out on samples after storing for 18 months at 2°C - 8°C along with freshly prepared products indicated no change in acute toxicity pattern.

EXAMPLES

The invention will now be illustrated by way of examples. The examples are by way of illustration only and in no way restrict the scope of the invention.

All the raw materials used in this example were of pharmaceutical grade. Equipments used were of conventional nature. Entire processing was done in an area with a controlled environment.

Example I

Two compositions were made with process runs A & B in this example. Process run B is comparative and not of the invention. Following ingredients were used in this example:

	Ingredients	A	B
a)	Propofol	1g	1g
b)	2-hydroxypropyl-β-cyclodextrin	30g	20g
c)	Glycerin	2.25g	2.25g
d)	Disodium edetate	0.005g	0.005g
e)	Water q.s.to	100ml	100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 55ml of Water at 25°C-30°C. Propofol was added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 3 hours maintaining the temperature at 25°C-30°C.

Glycerin and 0.5ml of Disodium edetate 1% w/v solution were added to the above solution under moderate stirring. The volume was made upto 100ml with water. The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

While the composition A remained clear on autoclaving, composition B became turbid. This example shows that the ratio of propofol to HPBCD is important to give composition stable to autoclaving.

Propofol content of the composition was determined by HPLC method using 270nm detector and a 4.6mm x 25cm column containing packing L1. The flow rate was adjusted to 1.5ml per minute. Mobile phase used consisted of water, acetonitrile and methanol in a volume ratio of 30:50:20.

The process run A giving composition having propofol content 10mg/ml was repeated on a larger batch and used for stability studies. Results of stability studies are presented in Table I.

Example II

Two compositions were made with process runs C & D in this example. Process run D is comparative and not of the invention. Following ingredients were used in this example:

	Ingredients	C	D
a)	Propofol	1g	1g
b)	2-hydroxypropyl-β-cyclodextrin	30g	20g

c)	Glycerin	2.25g	2.25g
d)	Disodium edetate	0.005g	0.005g
e)	Water q.s.to	100ml	100ml
f)	Dextrose solution5% q.s.to	500ml	500ml

Procedure :

Procedure followed was same as in Example I. However, after making up the volume to 100ml with water it was further diluted to 500ml with 5% Dextrose solution to bring propofol concentration to 2mg/ml. It was then filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved as per the procedure of Example I. While the composition (C) remained clear on autoclaving, composition (D) became turbid.

Propofol content of the composition was determined by the method specified under Example I.

The process run C giving composition having propofol content 2mg/ml was repeated on a larger batch and used for stability studies. Results of stability studies are presented in Table I.

The composition of Example II (C) was used in animal studies and the results are presented in Table II.

Example III

Two compositions were made with process runs E & F in this example. Process run F is comparative and not of the invention. Following ingredients were used in this example:

	Ingredients	E	F
a)	Propofol	0.2g	0.2g
b)	2-hydroxypropyl-β-cyclodextrin	6g	4g
c)	Glycerin	0.45g	0.45g
d)	Disodium edetate	0.001g	0.001g
e)	Dextrose	5g	5g
f)	Water q.s. to	100ml	100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 55ml of Water at 25°C-30°C.Propofol was added to HPBCD solution slowly under vigorous stirring at 25°C-30°C.

This solution was stirred at moderate speed for 3 hours maintaining the temperature at 25°C-30°C.

Glycerin and 0.1ml of Disodium edetate 1% w/v solution were added to the above solution under moderate stirring. Dissolve dextrose in 20ml of water and added to the above solution under moderate stirring. The volume was made upto 100ml with water. The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved. While the composition E remained clear on autoclaving, composition F became turbid.

This example shows that the ratio of propofol to HPBCD is important to give composition stable to autoclaving.

Example IV

Following ingredients were used in this example :

a) Propofol 1g
b) 2-hydroxypropyl-β-cyclodextrin 30g
c) Glycerin 2.25g
d) Disodium edetate 0.005g
e) Absolute alcohol (Ethanol) 62ml
f) Water q.s. to make 100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 60ml of Ethanol at 25°C-30°C. Propofol was dissolved in remaining quantity of Ethanol and added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for

15 minutes maintaining the temperature at 25°C-30°C. This alcoholic solution was rotary evaporated under vacuum, at 40°C to complete dryness.

The solid complex obtained was dissolved completely in 55ml of water to obtain a clear aqueous solution.

Glycerin and 0.5ml of disodium edetate 1% w/v solution were added to the above solution under moderate stirring. The volume was made upto 100ml with water.

The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

This composition remained clear on autoclaving.

Example V

Following ingredients were used in this example :

a) Propofol 0.2g
b) 2-hydroxypropyl-β-cyclodextrin 6g
c) Absolute alcohol (Ethanol] 13ml
d) Glycerin 0.45g
e) Disodium edetate 0.001g
f) Dextrose 5g
g) Water q.s. to make 100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 12ml of Ethanol at 25°C-30°C. Propofol was dissolved in remaining quantity of Ethanol and added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 15 minutes maintaining the temperature at 25°C-30°C. This alcoholic solution was rotary evaporated under vacuum, at 40°C to complete dryness.

The solid complex obtained was dissolved completely in 55ml of water to obtain a clear aqueous solution.

Glycerin and 0.1ml of disodium edetate 1% w/v solution were added to the above solution under moderate stirring.

The required quantity of Dextrose was dissolved in 30ml of water. Dextrose solution was added to the above solution under moderate stirring and the volume was made up to

100ml using water. The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

This composition remained clear on autoclaving.

Example VI

Three compositions were made with process runs G, H & I in this example. Process run H is comparative and not of the invention. Following ingredients were used in this example :

	Ingredients	G	H	I
a)	Propofol	1g	1g	1g
b)	2-hydroxypropyl-β-cyclodextrin	30g	20g	60g
c)	Water q.s. to	100ml	100ml	100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 55ml of Water at 25°C-30°C. Propofol was added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 3 hours maintaining the temperature at 25°C-30°C. The volume was made upto 100ml with water.

The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

While the composition G & I remained clear on autoclaving, composition H became turbid.

This example shows that the ratio of propofol to HPBCD is important to give composition stable to autoclaving.

Example VII

Following ingredients were used in this example :

a) Propofol 1g

b) 2-hydroxypropyl-β-cyclodextrin 30g

c) Potassium dihydrogen phosphate 0.476g

d) Sodium hydroxide 0.028g

e) Water q.s. to make 100ml

Procedure :

Buffer solution was prepared by dissolving Potassium dihydrogen phosphate and Sodium hydroxide in 55ml of water.

2-hydroxypropyl-β-cyclodextrin was dissolved in the above buffer solution at 25°C-30°C. Propofol was added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 3 hours maintaining the temperature at 25°C-30°C. The volume was made upto 100ml with water.

The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

This composition remained clear on autoclaving.

Example VIII

Following ingredients were used in this example :

a) Propofol 1g

b) 2-hydroxypropyl-β-cyclodextrin 30g

c) Absolute alcohol (Ethanol) 60ml

d) Water q.s. to make 100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 60ml of Ethanol at 25°C-30°C. Propofol was added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 15 minutes maintaining the temperature at 25°C-30°C. This alcoholic solution was rotary evaporated under vacuum, at 40°C to complete dryness.

The solid complex obtained was dissolved completely in 55ml of water to obtain a clear aqueous solution. The volume was made upto 100ml with water.

The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

This composition remained clear on autoclaving.

Example IX

Following ingredients were used in this example :

a) Propofol 1g

b) 2-hydroxypropyl-β-cyclodextrin 30g

c) Absolute alcohol (Ethanol) 2ml

d) Water q.s. to make 100ml

Procedure :

2-hydroxypropyl-β-cyclodextrin was dissolved in 55ml of water at 25°C-30°C.

Propofol was dissolved in 2ml of ethanol and added to HPBCD solution slowly under vigorous stirring at 25°C-30°C. This solution was stirred at moderate speed for 60 minutes maintaining the temperature at 25°C-30°C. This solution was rotary evaporated under vacuum, at 40°C to remove alcohol completely. The volume was made upto 100ml with water.

The clear solution obtained was filtered through 0.2μ filter, filled into glass vials under nitrogen, sealed and autoclaved.

This composition remained clear on autoclaving.

All the above mentioned Examples clearly indicate that complexation of propofol with 2-hydroxypropyl-β-cyclodextrin in 1:30 to 1:60 wt./wt. ratio makes the product stable to autoclaving.

TABLE - I

STABILITY DATA FOR PROPOFOL CLEAR SOLUTION

AT RECOMMENDED STORAGE TEMPERATURE OF 2°C-8°C

Duration ↓	Example I - Sample A (Propofol content 10mg/ml)		Example II - Sample C (Propofol content 2mg/ml)	
	Physical observation	Assay	Physical observation	Assay
Initial	Clear colourless solution	100.70%	Clear colourless solution	101.60%
6 Months	Clear colourless solution	100.22%	Clear colourless solution	99.80%
12 Months	Clear colourless solution	99.16%	Clear colourless solution	99.52%
18 Months	Clear colourless solution	98.73%	Clear colourless solution	98.65%

TABLE II

COMPARATIVE STUDY OF PROPOFOL CLEAR SOLUTION (PCS)* WITH PROPOFOL EMULSION (PE) FOR ONSET AND DURATION OF ANAESTHESIA IN MICE BY INTRAPERITONEAL ROUTE

Dose	10mg/kg		20mg/kg		40mg/kg		80mg/kg		120mg/kg	
Type of Product	PE	PCS	PE	PCS	PE	PCS	PE	PCS	PE	PCS
Onset time in Min.	**	2.32 to 2.84	**	0.73 to 1.93	**	0.52 to 1.23	1.60 to 3.30	0.20 to 1.06	0.50 to 1.54	0.17 to 0.95
Duration of anesthesia in min.	--	0.013 to 0.053	--	5.39 to 6.47	--	14.33 to 18.73	10.18 to 17.08	13.58 to 47.36	52.54 to 59.74	41.29 to 43.87

* Example II sample C

** No onset of action

Propofol emulsion (PE) - Prepared as per prior art containing Soybean oil & Egg phosphatide.

CLAIMS

1. An autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration comprising propofol and 2- hydroxypropyl - β - cyclodextrin (HPBCD) in a wt. ratio of propofol : HPBCD from about1:30 to about 1:60.

2. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in claim 1 wherein the composition further comprises other conventional additives as required by parenteral dosage form

3. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 2 wherein the content of propofol is from about 1mg/ml to about 20mg/ml.

4. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 3 wherein, the content of propofol is about 10mg/ml.

5. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 4 wherein, the content of propofol is about 2mg/ml.

6. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 5 wherein, the wt./wt. ratio of propofol to HPBCD used is about 1:30.

7. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 6 wherein, said other conventional additives required by parenteral dosage form are selected from a group of pharmaceutically acceptable additives such as anticrystallising agents, antioxidants, buffers and isotonic diluents.

8. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 7 wherein, said anticrystallising agents are selected from a group of pharmaceutically acceptable compounds such as Glycerin, Polyethylene glycol, Propylene glycol or a mixture thereof.

9. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 8 wherein, said antioxidants are selected from a group of pharmaceutically acceptable compounds such as Ethylene diamine tetraacetic acid and salts thereof, Sodium metabisulphite, Acetylcysteine, Ascorbic acid or a mixture thereof.

10. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 9 wherein, said buffer used is selected from a group of pharmaceutically acceptable buffers such as Phosphate buffers, Citrate buffers, Glycine buffers.

11. The autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1 - 10 wherein, said isotonic diluent used is Dextrose solution or Sodium chloride solution.

12. A process, for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1-11, comprising steps of

(i) addition of propofol as such or dissolved in a solvent to solution of 2-hydroxypropyl-β-cyclodextrin (HPBCD) either in water or other solvents in a wt. ratio of propofol : HPBCD from 1:30 to 1:60 under stirring;

(ii) keeping the said solution of propofol and HPBCD under intimate contact till complexation of propofol with HPBCD is complete to obtain a clear bulk solution;

(iii) removing said solvent if other than water, and adding water;

(iv) making up the volume with water to the required concentration of propofol in said composition;

(v) filtering the said composition obtained at the end of step (iv) through 2μ to 0.2μ filter;

(vi) filling the said filtrate obtained at the end of step (v) in containers such as vials, ampoules, followed by nitrogen purging and sealing the filled containers;

(vii) autoclaving the sealed containers filled with said filtrate.

13. The process, for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in claim 12, further comprising addition of conventional additives as required by parenteral dosage form, before filtration step.

14. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 or 13 wherein the content of propofol is from about 1mg/ml to about 20mg/ml.

15. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 14 wherein, the content of propofol is about 10mg/ml.

16. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 15 wherein, the content of propofol is about 2mg/ml.

17. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 16 wherein, the wt./wt. ratio of propofol to HPBCD used is about1:30.

18. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 17 wherein, propofol as such is added to HPBCD dissolved in water in step (i) of claim 12.

19. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 18 wherein, propofol as such is added to HPBCD dissolved in water in step (i) of claim 12 and the intimate contact as per step (ii) of claim 12 is brought about by using High shear mixer, Colloid mill or High pressure homogeniser.

20. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 19 wherein, for complexing with HPBCD, propofol dissolved in pharmaceutically acceptable organic solvents such as Ethanol, Methanol, Isopropyl alcohol or a mixture thereof is added to HPBCD solution in water in step (i) of claim 12.

21. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 20 wherein, propofol solution in Ethanol is added to HPBCD solution in water in step (i) of claim 12.

22. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 21 wherein, propofol as such is added to HPBCD dissolved in pharmaceutically acceptable organic solvents such as Ethanol, Methanol or a mixture thereof in step (i) of claim 12.

23. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 22 wherein, propofol as such is added to HPBCD dissolved in Ethanol in step (i) of claim 12.

24. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 23 wherein, for complexing with HPBCD, propofol dissolved in pharmaceutically acceptable organic solvents such as Ethanol, Methanol, Isopropyl alcohol or a mixture thereof is added to HPBCD solution in pharmaceutically acceptable organic solvents such as Ethanol, Methanol or a mixture thereof in step (i) of claim 12.

25. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 24 wherein, propofol as solution in Ethanol is added to HPBCD solution in Ethanol in step (i) of claim 12.

26. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 25 wherein, additives required by parenteral dosage form are selected from a group of pharmaceutically acceptable additives such as antioxidants, anticrystallising agents, buffers and isotonic diluents.

27. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 26 wherein, anticrystallising agents are selected from a group of pharmaceutically acceptable compounds such as Glycerin, Polyethylene glycol, Propylene glycol or a mixture thereof.

28. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 27 wherein, antioxidants are selected from a group of pharmaceutically acceptable compounds such as Ethylene diamine tetraacetic acid and salts thereof, Sodium metabisulphite, Acetylcysteine, Ascorbic acid or a mixture thereof.

29. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 28 wherein, buffer used is selected from a group of pharmaceutically acceptable buffers such as Phosphate buffers, Citrate buffers, Glycine buffers.

30. The process for preparation of a stable autoclaved clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 12 - 29 wherein, isotonic diluent used is Dextrose solution or Sodium chloride solution.

31. An autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration as claimed in any of claims 1-11 prepared by the process as claimed in any of claims 12 – 30.

32. An autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration substantially as herein described in the text and in the examples of the invention.

33. A process for preparation of a stable autoclaved clear aqueous composition of propofol, suitable for parenteral administration substantially as herein described in the text and in the examples of the invention.

34. An autoclaved stable clear aqueous pharmaceutical composition of propofol, suitable for parenteral administration prepared by the process substantially as herein described in the text and in the examples of the invention.

INTERNATIONAL SEARCH REPORT

ɪrnational Application No
PCT/IN 00/00124

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/05 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 32135 A (FARMARC NEDERLAND BV OF CITCO TRUST INTERNATIONAL MANAGEMENT) 17 October 1996 (1996-10-17) cited in the application claims 1-20	1-34

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2001	17/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Siatou, E

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TRAPANI G ET AL: "INCLUSION COMPLEXATION OF PROPOFOL WITH 2-HYDROXYPROPYL-BETA-CYCLODIXTRIN. PHYSICOCHEMICAL, NUCLEAR MAGNETIC RESONANCE SPECTROSCOPIC STUDIES, AND ANESTHETIC PROPERTIES IN RAT" JOURNAL OF PHARMACEUTICAL SCIENCES,US,AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, vol. 87, no. 4, 1 April 1998 (1998-04-01), pages 514-518, XP000739683 ISSN: 0022-3549 cited in the application abstract page 515, left-hand column	1-34
A	BIELEN S J ET AL: "THE EFFECT OF A CYCLODEXTRIN VEHICLE ON THE CARDIOVASCULAR PROFILE OF PROPOFOL IN RATS" ANESTHESIA AND ANALGESIA,XX,INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, vol. 82, no. 5, 1 May 1996 (1996-05-01), pages 920-924, XP002009539 ISSN: 0003-2999 abstract	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

ternational Application No
PCT/IN 00/00124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632135 A	17-10-1996	AU 5155096 A	30-10-1996
		ZA 9602214 A	07-10-1996